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| EXAMINER | |
|---|---|
| BERRIOS, JENNIFER A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1613 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/796,397 | FALOTICO ET AL. | |
| | Examiner | Art Unit | |
| | JENNIFER BERRIOS | 1613 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 March 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 6-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 6-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/7/2011*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

This office action is in response to the reply filed 3/22/2011, wherein claim 1 has been amended.

Currently claims 1 and 6-8 are pending examination.

### *Claim Objections*

Claim 1 is objected to because of the following informalities (underlined): "the concentration of rapamycin being the ithe range framo about 0.1 nanomolar to about 1 nanaomolar abd the concentration of topotecan being about 300 nanomolar; ". Appropriate correction is required. Objection necessitated by claim amendment.

### *Maintained Rejections*
### *Claim Rejections - 35 USC § 112*

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1 and 6-8 **remain** rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 1 has been amended to recite the rapamycin is present in a concentration of about 0.1 nanomolar to about 10 nanomolar, which does not find support in the specification. This is a new matter rejection, as the range of rapamycin claimed is not supported by the instant specification.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1 and 6-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 has been amended to recite "rapamycin being present in a concentration of about nanomolar to about 10 nanomolar." It is unclear what range of nanomolar concentrations are encompassed by the claims. Furthermore, claim 1 recited "chemically and physically incompatible chemistries," it is unclear what limitations this phrase is intended to convey.

***Claim Rejections - 35 USC § 103***

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1 and 6-8 **remain** rejected under 35 U.S.C. 103(a) as being unpatentable over Lentz et al (US 2002/0133183, pub. date: 9/19/2002), Eury (US 2002/0004679), Fischell et al (US 2003/0065382), Shull (WO 96/34003) and Mollison et al (US 2002/0123505).

For purposes of examination examiner will interpret "rapamycin being present in a concentration of about nanomolar to about 10 nanomolar" to mean a concentration ranging from 0 to about 10 nM.

Lentz teaches an implantable medical device that can be coated to minimize or substantially eliminate a biological organism's reaction to the introduction of the medical device to the organism. Therapeutic drugs may be mixed with the biocompatible materials and affixed at least to a portion of the medical device.

Regarding claim 1: The medical device can comprise a biocompatible vehicle, which comprises a polymeric matrix. The polymeric matrix can comprise a first and a second layer. The first layer comprises a therapeutic agent. The first layer can comprise a perfluoro copolymer comprising 55 to about 65% of polymerized residue of the vinylidenefluoride (VDF) copolymerized with from about 45 to about 35wt % of the polymerized residue of hexafluoropropylene (HFP) (claims 3, 5, 6, 10, 12 and [0084]). Fig. 6 demonstrates the release kinetics of rapamycin from poly (VDF/HFP). Additionally a top coating can be applied to delay the release of the pharmaceutical agent [0085]. For example, the outer layer can comprise only polybutylmethacrylate, which acts as a diffusion barrier to prevent the rapamycin from eluting

too quickly [0069]. Rapamycin is incorporated into the base layer [0069]. Example 3 demonstrates a stent having a coating.

Regarding the phrase "chemically and physically incompatible chemistries," as the prior art teaches the first and second polymeric materials as defined by spec, this limitation is considered to be taught.

Regarding claims 6-8: The coating and drugs may be utilized and combined with medical devices such as stents and stent-grafts. Other medical devices include vena cava filters and anastomosis devices [0130].

Lentz fails to teach the medical device to comprise topotecan in combination with rapamycin in the basecoat in the concentrations recited by instant claim 1.

Fischell teaches a stent that is coated with a composition comprising a polymer and one or more anti-restenosis drugs (basecoat matrix) selected from the group consisting of a finite amount of particular drugs including topoisomerase I inhibitors including adriamycin etoposide, irinotecan and hycamptin (topotecan) as well as rapamycin (abstract; paragraphs [0020] and [0022]). Furthermore the stent is coated with a plastic material selected from parylene, silicone rubber, polyurethane, polyethylene, nylon and PTFE (polytetrafluoroethylene), a fluoro polymer, wherein the anti-restenosis drug is diffused into the plastic coating (claims 2-3 and 7-8).

Eury teaches the use of topoisomerase inhibitors for the prevention of restenosis. The method includes administering a topoisomerase inhibitor on a stent for local administration (Abstract). The topoisomerase inhibitor is selected from camptothecin, irinotecan and topotecan. In one embodiment the polymer stent is loaded with camptothecin, irinotecan or topotecan (Pg 1 [0015]). A second active agent can be co-administered with the topoisomerase inhibitor, such as Paclitaxel (Pg 1 [0017]), well known to those of ordinary skill in the art to aid in the prevention of restenosis (Pg 2 [0022]).

One of ordinary skill in the art would have been motivated to combine rapamycin and topotecan because as suggested by Fischell because they are all art-recognized equivalents used for the same purpose. All references teach coating an implantable medical device with a composition comprising anti-restenosis drugs, thus one skilled in the art would readily look to Lentz/Fischell for other anti-restenosis drugs or combinations of anti-restenosis drugs as substitutions to achieve the predictable result of generating a medical device with the desired anti-restenosis drugs. A practitioner would have reasonably expected a medical device coated with a sustained release coating comprising a combination of anti-restenosis drugs such as a topoisomerase I inhibitor, specifically topotecan, camptothecin or irinotecan as taught by Eury, and a rapamycin to be successful, absent evidence to the contrary..

Lentz/Fischell/Eury fail to teach the specific concentration of topotecan recited.

Shull teaches chemotherapeutic agents, such as camptothecin, being delivered in vivo to fight cancer growth in the body. For in vivo cell inhibition assays, camptothecin was found to have the following 50% cell growth inhibition concentration (Table 4) ranging from 5.74 nm to about 3223.7nm depending on the cell line.

It would have been prima facie obvious to one of skill in the art at the time the invention was made utilize topotecan in the concentrations taught by Shull dependent on the desired results. One of ordinary skill in the art would have been motivated to do so because topotecan and camptothecin are art-recognized equivalents, both topoisomerase I inhibitors, useful on polymeric stents for the treatment of restenosis, furthermore it would have been obvious to vary the concentration of topotecan used depending on the cell line looking to inhibit as Shull teaches that different cell lines require different concentration to achieve 50% inhibition.

Lentz/Fischell/Eury and Shull do not teach the specific concentration of rapamycin recited.

Mollison teaches that rapamycin and rapamycin compounds are effective immunomodulators. Rapamycin has been shown to reduce neointimal proliferation in animal models, and to reduce the rate of restenosis in humans [0008]. Suitable immunoeffective concentrations of rapamycin are 0.91 +/- 0.36 nM (Table 1).

It would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to combine the teachings of Lentz/Fischell/Eury/Shull and Mollison. One of skill in the art would have been motivated to use the rapamycin taught by Lentz/Fischell/Eury/Shull on nanomolar concentrations of 0.91 +/- 0.36, as Mollison discloses that these concentrations are necessary for effective immunomodulation and further discloses that the rapamycin is effective at treating restenosis. Finally one of skill in the art would have a reasonable expectation of success as both Lentz/Fischell/Eury/Shull and Mollison teach medical devices having rapamycin or rapamycin compounds that are effective at treating restenosis.

Regarding claim 1: Although the prior art does not specifically disclose that PVDF/HFP and BMF are immiscible, "which when mixed together and precipitated from a solution undergo phase separation thereby creating a physical chemical barrier to drug elution," this property is inherent in the polymers recited by instant claim 1.

***Response to Arguments***

Applicant argues that the date from Fig. 64 shows the concentration of rapamycin starting from about 1*10-10 or 0.1 nanomolar and rising, thus providing support for the claimed nanomolar range of rapamycin.

This is not persuasive. While the label on the axis of Fig. 64 embraces the claimed range, the individual data points present in the figure do not correspond to this range, therefore there is no reason to believe based on this figure alone that the claimed range is contemplated by the instant disclosure.

Applicant argues that the references taken as a whole fail to disclose or even suggest a medical device with two specific drugs in a specific dosage in a two distinct polymer structure with a specific polymer ratio. None of the references taken as a whole disclose the use of immiscible polymers on the same device as claimed. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

This is not persuasive, The combination of prior art references, as discussed in the advisory action mailed 6/22/2010 and the office action mailed 4/12/2010, specifically page 4, discloses an implantable structuring having a basecoat matrix comprising polyvinyledinefluoride and hexafluoropropylene (PVDF/HFP) in a 60/40 weight ratio and a top coat comprising polybutylmethacrylate (BMA). Although the prior art does not specifically disclose that these polymers are immiscible, the instant specification discloses that PVDF/HFP and BMF are immiscible or incompatible polymers (Paragraph 0411). The drug dosages of topotecan (nanomolar concentration) are specifically addressed in page 6 of the office action mailed 4/12/2010.

## ***Conclusion***

No claims are allowable.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER BERRIOS whose telephone number is (571)270-7679. The examiner can normally be reached on Monday-Thursday: 7:00am-4:00pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Kwon can be reached on (571) 272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer A Berrios/
Examiner, Art Unit 1613

/Tracy Vivlemore/
Primary Examiner, Art Unit 1635